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IN THE SPECIFICATION

At page 4, line 21 through page 5, line 9, please replace paragraphs with the following text:

The present invention is based, in part, on the discovery of a novel full-length human gene referred to herein as "MEKK1". The polynucleotide sequence of a cDNA encoding a MEKK1 polypeptide is shown in SEQ ID NO:1, and the amino acid sequence of a MEKK1 polypeptide is shoen in SEQ ID NO:2. In addition, the polynucleotide sequence of the coding region is from nucleotide 7 to nucleotide 4545 of SEQ ID NO:1. ~~depicted in SEQ ID NO:3.~~

Accordingly, in a first aspect, the invention features a full-length nucleic acid molecule which encodes a MEKK1 protein or polypeptide, e.g., a biologically active portion of the MEKK1 protein. In a preferred embodiment the isolated nucleic acid molecule encodes a polypeptide having the amino acid sequence of SEQ ID NO:2. In other embodiments, the invention provides isolated MEKK1 nucleic acid molecules having the polynucleotide sequence shown in SEQ ID NO:1, or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1, ~~SEQ ID NO:3,~~ or the sequence of the DNA insert of the plasmid deposited with ATCC Accession Number PTA-1836. In still other embodiments, the invention provides nucleic acid molecules that are substantially identical (e.g., naturally occurring allelic variants) to the nucleotide sequence shown in SEQ ID NO:1, or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1, ~~SEQ ID NO:3,~~ or the sequence of the DNA insert of the plasmid deposited with ATCC Accession Number PTA-1836. In other embodiments, the invention provides a nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO:1 or the sequence of the DNA insert of the plasmid deposited with ATCC Accession Number PTA-1836, wherein the nucleic acid encodes a full-length MEKK1 protein or an active fragment thereof.

At page 6, lines 3-13, please replace the paragraph with the following text:

In another embodiment of the second aspect, the invention provides MEKK1 polypeptides, e.g., a MEKK1 polypeptide having the amino acid sequence shown in SEQ ID NO:2; the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC Accession Number PTA-1836; an amino acid sequence that is substantially identical to the amino acid sequence shown in SEQ ID NO:2; or an amino acid sequence encoded by a nucleic acid molecule having a polynucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~3~~, or the sequence of the DNA insert of the plasmid deposited with ATCC Accession Number PTA-1836, wherein the nucleic acid encodes a full length MEKK1 protein or an active fragment thereof.

At page 7, lines 18-22, please replace the paragraph with the following text:

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Figure 1 depicts the nucleic acid sequence (SEQ ID NO:1) of human MEKK1 and the predicted amino acid sequence (SEQ ID NO:2) of human MEKK1. The methionine-initiated open reading frame of human MEKK1 ~~is shown in SEQ ID NO:3, and~~ starts at nucleotide 7 and goes to nucleotide 4545 of SEQ ID NO:1.

At page 8, lines 13-22, please replace the paragraph with the following text:

The human full-length MEKK1 nucleic acid sequence (Figure 1; SEQ ID NO:1), which is approximately 5245 nucleotides long including untranslated regions, contains a predicted methionine-initiated coding sequence of about 4536 nucleotides (nucleotides 7-4545 of SEQ ID NO:1~~, which correspond to nucleotides 1-4539 of SEQ ID NO:3~~). As used herein, "MEKK1 nucleic acid" and "MEKK1 gene" comprise nucleic acid sequences 1-5245 of SEQ ID NO:1. The coding sequence encodes a 1512 amino acid protein (SEQ ID NO:2). The open reading frame (ORF) analysis of the human MEKK1 protein of SEQ ID NO:2 indicates that the protein does not include a signal sequence nor does it include any transmembrane domains.

At page 15, line 11 through page 16, line 4, please replace the paragraph with the following text:

As used herein, the term "hybridizes under stringent conditions" describes conditions for hybridization and washing. Stringent conditions are known to those skilled in the art and can be found, e.g., in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Aqueous and nonaqueous methods are described in that reference and either can be used. A preferred example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50°C. Another example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 55°C. A further example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 60°C. Preferably, stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C. Particularly preferred stringency conditions (and the conditions that should be used if the practitioner is uncertain about what conditions should be applied to determine if a molecule is within a hybridization limitation of the invention) are 0.5M Sodium Phosphate, 7% SDS at 65°C, followed by one or more washes at 0.2X SSC, 1% SDS at 65°C. Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1~~3~~, corresponds to a naturally-occurring nucleic acid molecule.

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At page 16, line 26 through page 17, line 24, please replace the paragraphs with the following text:

A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of MEKK1 (e.g., the sequence of SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836) without abolishing or, more preferably, without substantially altering a biological activity of MEKK1, whereas an "essential" amino acid residue results in such a change. For example, amino acid residues that are conserved among the polypeptides of the present invention are predicted to be particularly unamenable to alteration.

A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a MEKK1 protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a MEKK1 coding sequence, such as by saturation mutagenesis, and the resultant mutant polypeptides can be screened for MEKK1 biological activity to identify mutant polypeptides that retain activity. Following mutagenesis of SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

At page 21, line 17 through page 23, line 7, please replace the paragraphs with the following text:

In one embodiment, an isolated nucleic acid molecule of the invention includes the nucleotide sequence shown in SEQ ID NO:1, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836, or a portion of any of these nucleotide sequences. In one embodiment, the nucleic acid molecule includes sequences encoding the human MEKK1 protein (i.e., "the coding region", from nucleotides 7-4539 of SEQ ID NO:1), as well as 5' untranslated sequence corresponding to nucleotides 1-6 of SEQ ID NO:1 and 3' untranslated sequence corresponding to nucleotides 4546 to 5245 of SEQ ID NO:1. Alternatively, the nucleic acid molecule can include only the coding region of SEQ ID NO:1 (e.g., nucleotides 7-4545~~, corresponding to nucleotides 1-4539 of SEQ ID NO:3~~) and, e.g., no flanking sequences which normally accompany the subject sequence. In another

embodiment, the nucleic acid molecule encodes a sequence corresponding to the mature protein from about amino acid 1 to amino acid 1512 of SEQ ID NO:2.

In another embodiment, an isolated nucleic acid molecule of the invention includes a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 3, or the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836, or a portion or fragment of any of these nucleotide sequences. In other embodiments, the nucleic acid molecule of the invention is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 3, or the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836 such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 3, or the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836, thereby forming a stable duplex.

In one embodiment, an isolated nucleic acid molecule of the present invention includes a nucleotide sequence which is at least about: 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more homologous to the entire length of the nucleotide sequence shown in SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 3, or the entire length of the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836, or a portion, preferably of the same length, of any of these nucleotide sequences.

MEKK1 Nucleic Acid Fragments

A nucleic acid molecule of the invention can include only a portion of the nucleic acid sequence of SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 3, or the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836. For example, such a nucleic acid molecule can include a fragment that can be used as a probe or primer or a fragment encoding a portion of a MEKK1 protein, e.g., an immunogenic or biologically active portion of a MEKK1 protein. A fragment can comprise nucleotides 3576-4542 of SEQ ID NO:1, which encodes a kinase or catalytic domain of human MEKK1. A fragment can comprise nucleotides 2632-4542 of SEQ ID NO:1, which encodes a cleaved/processed domain of human MEKK1. The nucleotide sequence determined from the cloning of the MEKK1 gene allows for the generation of probes and primers designed for use in identifying and/or cloning other MEKK1 family members, or fragments thereof, as well as MEKK1 homologues, or fragments thereof, from other species.

At page 25, lines 15-24, please replace the paragraph with the following text:

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MEKK1 probes and primers are provided. Typically a probe/primer is an isolated or purified oligonucleotide. The oligonucleotide typically includes a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense or antisense sequence of SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836, or of a naturally occurring allelic variant or mutant of SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836.

At page 26, lines 18-30, please replace the paragraph with the following text:

A nucleic acid fragment encoding a "biologically active portion of a MEKK1 polypeptide" can be prepared by isolating a portion of the nucleotide sequence of SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~3~~, or the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836, which encodes a polypeptide having a MEKK1 biological activity (e.g., the biological activities of the MEKK1 proteins are described herein), expressing the encoded portion of the MEKK1 protein (e.g., by recombinant expression *in vitro*) and assessing the activity of the encoded portion of the MEKK1 protein. For example, a nucleic acid fragment encoding a biologically active portion of MEKK1 includes a protein kinase domain, e.g., amino acid residues 1191 to 1512 of SEQ ID NO:2. A nucleic acid fragment encoding a biologically active portion of a MEKK1 polypeptide, may comprise a nucleotide sequence which is greater than 900 or more nucleotides in length.

At page 27, lines 3-15, please replace the paragraph with the following text:

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~3~~, or the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836. Such differences can be due to degeneracy of the genetic code and result in a nucleic acid which encodes the same MEKK1 proteins as those encoded by the nucleotide sequence disclosed herein. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence which differs, by at least 1, but less than 5, 10, 20, 50, 75, or 100 amino acid residues from that shown in SEQ ID NO:2. If alignment is needed for this comparison the sequences should be aligned for maximum homology. "Looped" out sequences from deletions or insertions, or mismatches, are considered differences.

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At page 28, lines 1-18, please replace the paragraphs with the following text:

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 3, or the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836. Such differences can be due to degeneracy of the genetic code and result in a nucleic acid which encodes the same MEKK1 proteins as those encoded by the nucleotide sequence disclosed herein. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence which differs, by at least 1, but less than 5, 10, 20, 50, 75, or 100 amino acid residues from that shown in SEQ ID NO:2. If alignment is needed for this comparison the sequences should be aligned for maximum homology. "Looped" out sequences from deletions or insertions, or mismatches, are considered differences.

Orthologs, homologs, and allelic variants can be identified using methods known in the art. These variants comprise a nucleotide sequence encoding a polypeptide that is 50%, at least about 55%, typically at least about 70-75%, more typically at least about 80-85%, and most typically at least about 90-95% or more, identical to the amino acid sequence shown in SEQ ID NO:2 or a fragment of this sequence. Such nucleic acid molecules can readily be identified as being able to hybridize under stringent conditions, to the nucleotide sequence shown in SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1, or a fragment of the sequence. Nucleic acid molecules corresponding to orthologs, homologs, and allelic variants of the MEKK1 cDNAs of the invention can further be isolated by mapping to the same chromosome or locus as the MEKK1 gene.

At page 29, lines 17-21, please replace the paragraph with the following text:

Moreover, nucleic acid molecules encoding other MEKK1 family members and, thus, which have a nucleotide sequence which differs from the MEKK1 sequences of SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 3, or the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as Accession Number PTA-1836 are intended to be within the scope of the invention.

At page 30, lines 8-18, please replace the paragraph with the following text:

In another aspect, the invention features, an isolated nucleic acid molecule which is antisense to MEKK1. An "antisense" nucleic acid can include a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, e.g., complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. The antisense nucleic acid can be complementary to an entire MEKK1 coding strand, or to only a portion thereof (e.g., the coding region of

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human MEKK1 corresponding to nucl otide 7 to nucleotide 4545 of SEQ ID NO:1 ~~SEQ ID NO:3~~). In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding MEKK1 (e.g., the 5' and 3' untranslated regions).

At page 32, lines 5-17, please replace the paragraph with the following text:

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. A ribozyme having specificity for a MEKK1-encoding nucleic acid can include one or more sequences complementary to the nucleotide sequence of a MEKK1 cDNA disclosed herein (i.e., SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~3~~), and a sequence having known catalytic sequence responsible for mRNA cleavage (see U.S. Pat. No. 5,093,246 or Haselhoff and Gerlach (1988) *Nature* 334:585-591). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a MEKK1-encoding mRNA. (See, e.g., Cech et al., U.S. Patent No. 4,987,071; and Cech et al., U.S. Patent No. 5,116,742.) Alternatively, MEKK1 mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. (See, e.g., Bartel et al., *Science* 261:1411-1418. (1993))

At page 65, line 21 through page 66, line 2, please replace the paragraph with the following text:

Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. The noncoding sequences of SEQ ID NO:1 can provide positive individual identification with a panel of perhaps 10 to 1,000 primers which each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences, such as those in nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~SEQ ID NO:3~~ are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

At page 68, lines 3-10, please replace the paragraph with the following text:

For example, detecting the genetic lesion can include: (i) providing a probe/primer including an oligonucleotide containing a region of nucleotide sequence which hybridizes to a sense or antisense sequence from SEQ ID NO:1 or nucleotide 7 to nucleotide 4545 of SEQ ID NO:1 ~~SEQ ID NO:3~~, or naturally occurring mutants thereof, or 5' or 3' flanking sequences naturally associated with the MEKK1 gene; (ii) exposing the probe/primer to nucleic acid of the tissue; and detecting, by hybridization, e.g., *in situ* hybridization, of the probe/primer to the nucleic acid, the presence or absence of the genetic lesion.

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At page 104, lines 17-22, please replace the paragraph with the following text:

The human MEKK1 sequence, (Figure 1; SEQ ID NO:1), which is approximately 5245 nucleotides long, including untranslated regions, contains a predicted methionine-initiated coding sequence of about 4539 nucleotides (nucleotides 7- 4542 of SEQ ID NO:1~~, which corresponds to numbered nucleotides 1- 4539 of SEQ ID NO:3~~). The coding sequence encodes a 1512 amino acid protein (SEQ ID NO:2).